**Remarks/Arguments:**

Claims 67-106, newly presented, are pending, with claims 32-35, 41-42, 49, 52, 57, 59, 64, and 66 standing withdrawn, pursuant to restriction.

Claims 1-66 are cancelled, without prejudice or disclaimer.

Present claims 67-106 correspond to claims 27-66, respectively, amended to more clearly define the present invention, as further explained below.

The rejection of claim 30 under 35 U.S.C. 112, second paragraph, is rendered moot in view of present, replacement claim 70. Withdrawal of the rejection appears to be in order.

Claims 27-29, 31, 36, 43 and 45 are rejected under 35 U.S.C. 102(e) as being allegedly anticipated U.S. 2003/0206887 (Morrissey). Reconsideration is requested.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the claim, must be found in a single prior art reference. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). The "absence" from a prior art reference of a single claim limitation "negates anticipation." *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81, 84 (Fed. Cir. 1986). To anticipate the claim, each claim limitation must "identically appear" in the reference disclosure, *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997), and the reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985).

According to the rejection, the rejected claims are anticipated by the Morrissey description of sequences comprising SEQ ID NO. 2 and 3. More particularly, the PTO alleges that Morrissey

sequences 919 and 931 would comprise SEQ ID NO. 2 and that Morrissey sequence 1380 is identical to SEQ ID NO: 3.

Morrissey describes small interfering molecules of nucleic acids (siNA and siRNA) capable of reducing the expression of the hepatitis B viral genes by "RNA interference" (RNAi). The reference does not teach or suggest that these nucleic acids could be used as primers during amplification of nucleic acids. More importantly, the nucleic acids described by Morrissey are ribonucleic acids, *i.e.,* RNA.

On the other hand, the present claims are limited to "DNA." As such, the "absence" of the DNA limitation from Morrissey "negates anticipation" of claims 67-75 by Morrissey. *Kolster Speedsteel AB,* 230 USPQ at 84.

In view of the foregoing remarks, the rejection of claims 27-29, 31, 36, 43, and 45 under §102(e), as allegedly anticipated by Morrissey, is overcome. Withdrawal of the rejection appears to be in order.

Claims 27-29, 31, 36-40, 43-46, 48, 50, 51, 53-56 and 58 are rejected under 35 U.S.C. 103(a) as being allegedly anticipated over Saito as evidenced by Heid and the GenBank sequence, Higashi, Stoll-Becker, Su and Buck. Claims 60-63 and 65 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Saito as evidenced by Heid and the GenBank sequence, Higashi, Stoll-Becker, Su, Buck, U.S. Patent No. 6,635,428 (Pasupuletti) and Stratagene. Reconsideration is of the rejections requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art," *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970), "and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002).

When the claimed invention requires modification of the prior art, there is no obviousness under §103 when "[t]he prior art does not suggest . . . [the] modification . . . or provide any reason or motivation to make the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

> The mere fact that it is possible to find two isolated disclosures which might be combined in such a way as to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination.

*In re Bergel*, 130 USPQ 206, 208 (CCPA 1961).

> A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art . . . , However, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

*In re Kahn*, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

A *reasonable expectation of success* is only part of what the PTO must demonstrate to support a rejection for obviousness under §103(a): "Both *the suggestion* and reasonable expectation

of success must be founded in the prior art." *In re Vaeck*, 20 USPQ2d 1438, 1441 (Fed. Cir. 1991) (*emphasis added*). Even assuming, arguendo, a reasonable expectation of success, as alleged in the statement of rejection, were "founded in the prior art," this still fails to support the rejection, because the requisite "suggestion" is not also found in the prior art. *Id.*

"It is facts which must support the legal conclusion of obviousness." *Ex parte Crissy*, 201 USPQ 689, 695 (POBdApp 1976).

> The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it* may *doubt* that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

*In re Warner*, 154 USPQ 173, 178 (CCPA 1967) (*emphasis original*). An argument by the USPTO is "not prior art." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

Saito teaches the quantification of the HBV DNA by quantitative RT-PCR. The Saito probe is not the "DNA" to which the present claims are limited. The probe used by Saito is complementary to a HBV DNA fragment, which is absent from in the DNA amplified with the primers as presently claimed. Saito detects the presence of the HBV DNA, the mean value of the obtained concentration of the HBV DNA being $1.8 \times 10^3$ copies/ml.

Saito does not teach primers and probes comprising SEQ ID NO. 2, 3 or 8. However, the PTO alleges that it would have been obvious to identify the sequences of alternative probes and primers, with reasonable chance of success.

First of all, the rejection cannot be maintained because the requisite motivation for combining prior art references to establish obviousness is missing. Even assuming, arguendo, that one of

ordinary skill in the art would expect the (alleged) alternative probes and primers (for those described in Saito) to function in Saito with a reasonable expectation of success, this begs the question of motivation; that is, the PTO has failed to provide the requisite motivation (*i.e.*, desirability) for one skilled in the art to have used the alternative probes and primers (in Saito), in the first place.

> In a situation where
>
> > the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at . . . [the claimed] invention because he had the necessary skills to carry out the requisite process steps[,] [t]his is an inappropriate standard for obviousness.

*Ex parte Levengood*, 28 USPQ2d 1300, 1301 (BPA&I 1993). "That which is within the capabilities of one skilled in the art is not synonymous with obviousness [citations omitted]." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993).

> We have previously rejected the argument that undirected skill of one in the pertinent art is an adequate substitute for statutory prior art [*citation omitted*].

*In re Kratz*, 201 USPQ 71, 76 (CCPA 1979).

> The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

*In re Fritch*, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992).

> The mere fact that it is possible to find two isolated disclosures which might be combined in such a way as to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination.

*Bergel*, 130 USPQ at 208.

Secondly, attention is directed to the fact that probes and primers according to the presently claimed invention are not alternative probes and primers to those of Saito but improved probes and primers. Indeed, Saito only studies the case of 2 patients considered as not bearing the B or C variants of HBV. Therefore this document does not describe oligonucleotides allowing detecting all the HBV variants. To the contrary, the oligonucleotides recited in the present claims allow the detection of all the (A to G) HBV variants with the same efficiency (see table 1, page 13 and lines 1-2, page 14).

Furthermore, attention is directed to the lack of experimental data described by Saito, so the sensibility of the Saito method of detection used on a wide range of concentrations of the HBV DNA varying between $10^2$ and $10^9$ copies/ml cannot be validated, such as described in the present application (page 14, line 25). Indeed, the values punctually detected by Saito only vary between 250 and 2600 copies/ml (figure 1, page 328).

Therefore, the presently claimed invention provides at least two advantageous effects over the method of Saito, namely the detection of very low circulating quantities of virus ($10^2$ - $10^3$ /ml), and also the detection of all HBV variants (A to G).

Additionally, applicants find that neither Saito nor any of the cited secondary references—taken alone or in combination—teaches or suggests how to obtain probes and primers allowing an improved detection of HBV by RT-qPCR. To reject claims for obviousness under §103 based on modifying the teachings of a reference, existence in the prior art of a reason (motivation) to effect

the modification is not, by itself, sufficient to sustain the initial burden on the PTO; the "record" must show

> . . . that it would also have been obvious *how* this [modification] could be achieved . . . . Obviousness . . . must not be judged by hindsight, and a "little modification" can be a most unobvious one.

*In re Irani*, 166 USPQ 24, 27 (CCPA 1970) (*emphasis in original*). Prior art relied on in a rejection under §103 must be *enabling*, i.e., "if the prior art of record fails to disclose or render obvious a method of making the claimed [invention] . . . it may not be legally concluded that the compound was in the possession of the public. *In re Hoeksema*, 158 USPQ 596, 601 (CCPA 1968).

For example:

– Heid is a review that relates to RT-qPCR, and do not concern probes and primers to detect HBV;

– GenBank entry N°X98077 describes the sequence of the HBV genome, but does not describes probes and/or primers allowing detecting HBV;

– Higashi, Stoll-Becker and Known do not teach that their primers allow detecting the HBV genome on a wide range of concentrations, since the sensibility of detection of the methods disclosed in these documents have not been studied by the authors;

– Buck is a review dealing with the strategy of selection of primers used to sequence a DNA fragment. This review does not relate to the strategy of selection of primers and probes for detection of HBV by RT-qPCR. Moreover, this document does not describe the detection of all the HBV variants with the same efficiency.

Therefore, none of the above documents teaches nor suggests how to obtain primers and probes allowing detecting HBV on a wide range of concentrations of DNA, with an improved sensibility with regard to Saito and in addition allowing to detect all HBV variants.

Moreover, attention is directed to the fact that the conclusions of Buck are not applicable to the present case.

Indeed, Buck teaches the results of a survey analyzing the strategies of selection of primers for sequencing and estimates the performance of these primers. To realize this survey, a "test sequence" of DNA of 300 pairs of bases was sent to the participants, who had to create and submit 5' primers (sense) allowing the sequencing of the test sequence. The survey showed that each of the primers submitted by the participants, as well as each of the primers used as control, worked. The examiner concludes that any primer, and in particular those chosen according to the common criteria, may allow elongation of a given DNA sequence.

Applicants further draw attention to:

– The test sequence used by Buck is an "ideal" synthetic sequence, which contains no region susceptible to affect elongation, and not a region of the HBV genome susceptible to contain repetitions or secondary structures which can render more difficult hybridization of the primers and elongation.

– The participants of the survey were free to place their primers wherever they wished in the proposed test sequence. Buck note, that apparently, certain segments of the sequence were voluntarily excluded by the participants. On the contrary, in the case of detection of HBV, the choice

of the segment to be amplified is essential to allow the detection of all the genotypes of the HBV and any fragment cannot be chosen.

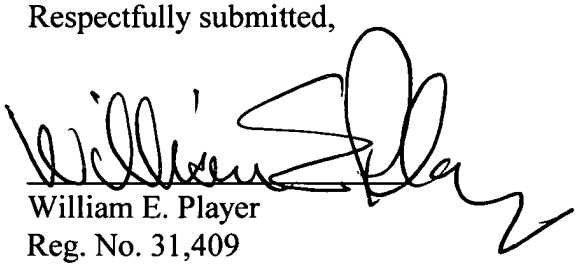
– The participants of the survey had to design only 5' primers to be used only for a sequencing, which an amplification by PCR requires a couple of primers with compatible physical and chemical characteristics. Generally speaking, the choice of a couple of primers is subjected to requirements concerning their length, their Tm, their percentage in G-C, the absence of repetitions and secondary structures, the presences of G-C nucleotides in 3', the low chance that these primers form dimers of primers and the compatibility of both primers of the same couple (in particular, same Tm, the same conditions of PCR).

– So, the conclusions of Buck allow by no means concluding that it is obvious to obtain probes and primers allowing detecting HBV by RT-qPCR. Buck does not allow concluding that it is obvious to obtain probes and primers allowing HBV with an improved sensibility, either. Moreover, Buck does not allow concluding that it is obvious to obtain probes and primers suitable for detecting all HBV variants.

In view of the foregoing remarks, the rejections of claims 27-29, 31, 36-40, 43-46, 48, 50, 51, 53-56, 58, 60-63, and 65 under §103(a) are overcome. Withdrawal of the rejections appears to be in order.

Favorable action is requested.

Respectfully submitted,



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